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(54) **Title:** NOVEL ANIT-INFECTIVES

(57) **Abstract:** Disclosed are compounds useful as HCV anti-infectives and methods of making and using the same.

NOVEL ANTI-INFECTIVES

FIELD OF THE INVENTION

The present invention relates to compounds that inhibit an RNA-containing virus and methods of making and using the same. Specifically, the present invention relates to inhibitors of hepatitis C virus (HCV).

BACKGROUND OF THE INVENTION

In the U.S., an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at $5.46 billion for the U.S. in 1997. Worldwide, over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/yr. by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, and depression from interferon, as well as hemolytic anemia induced by ribavirin (Lindsay, K.L. (1997) Hepatology 26 (Suppl. 1):71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of those treated, 50-70% relapse within 6 months of cessation of treatment. Recently with the introduction of pegylated interferon (Peg-IFN), both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L. *et al.*, (1989) Science 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo,G. *et al.*, (1989) Science 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in

the *Flaviviridae* family. Like the other members of the *Flaviviridae* (such as flaviviruses (e.g., yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g., bovine viral diarrhea virus, border disease virus, and classic swine fever virus (Choo *et al.*, 1989; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061)), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang, C.Y., Le, S.Y., Ali, N., Siddiqui, A., Rna-A Publication of the Rna Society. 1(5): 526-537, 1995 Jul). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, the HCV-RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (Eds.) Virology, 2nd Edition, p931-960, Raven Press, NY). Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. *et al.*, (1996) J. Virology 70:3363-3371; Tanaka, T. *et al.*, (1995) Biochem Biophys. Res. Commun. 215:744-749; Tanaka, T. *et al.*, (1996) J. Virology 70:3307-3312; Yamada, N. *et al.*, (1996) Virology 223:255-261). The 3' NTR is predicted to form a stable secondary structure that is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

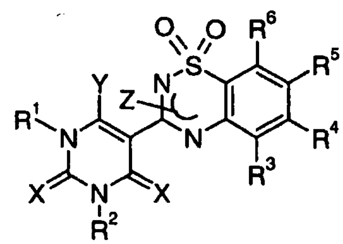
The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E., *et al.*, (1996) EMBO J. 15:12-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (Kolykhalov, A.A., *et al.*, (2000) J. Virology 74:2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to cure HCV infection.

Positive strand hepatitis C viral RNA is the nucleic acid strand that is translated and initially copied upon entry of the HCV-RNA into the cell. Once in the cell, positive strand viral RNA generates a negative strand replicative intermediate. Negative strand RNA is the template used to generate the positive strand message that is generally packaged into productive virions. Presently, HCV inhibitor compounds are only evaluated for their ability to inhibit positive strand HCV-RNA. However, it would be desirable to develop inhibitor compounds having the ability to inhibit both positive and negative strand replication to obtain complete clearance of the HCV virus.

Accordingly, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit HCV. Preferably, such synthetic or biological compounds inhibit both positive and negative strand replication of the hepatitis C virus.

SUMMARY OF THE INVENTION

This invention is directed to compounds having Formula I, as follows:



I

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C(O)OR^7, -C(O)R^7, and -C(O)NR^{7}R^8 , where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC$_1$-C$_4$ alkyl, -SC$_1$-C$_4$ alkyl, -NR^{8}R^9, cyano, nitro, -CO$_2$R^8, -C(O)OC$_1$-C$_4$ alkyl, -CONR^{8}R^9, -CONH$_2$, aryl, and heteroaryl, or said cycloalkyl, heterocycloalkyl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, -NH$_2$, -OC$_1$-C$_4$ alkyl, -SC$_1$-C$_4$ alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano, nitro, -CO$_2$H, -C(O)OC$_1$-C$_4$ alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl) and -CONH$_2$;

R^2 is hydrogen, -C(O)OR^9, C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, -(C_1-C_6 alkyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkenyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkynyl)-(C_3-C_6 cycloalkyl), -(C_1-C_6 alkyl)-heterocycloalkyl, -(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl,

where said C_2-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, -OC_1-C_4 alkyl, -SH, -SC_1-C_4 alkyl, -S(O)(C_1-C_4 alkyl), -SO_3H, and -S$(O)_2$(C_1-C_4 alkyl),

said C_3-C_6 cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_4 alkyl, -OH, -OC_1-C_4 alkyl, -SH, -SC_1-C_4 alkyl, -S(O)(C_1-C_4 alkyl), -SO_3H, and -S$(O)_2$(C_1-C_4 alkyl),

or the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said -(C_1-C_6 alkyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkenyl)-(C_3-C_6 cycloalkyl), -(C_2-C_6 alkynyl)-(C_3-C_6 cycloalkyl), -(C_1-C_6 alkyl)-heterocycloalkyl, -(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, -NH_2, -OC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -NH(C_1-C_4 alkyl);

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6 alkyl, -OH, and -OC_1-C_4 alkyl;

R^5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, nitro, cyano, halogen, -C(O)OR^7, -C(O)R^7, -C(O)NR^7R^8, -OR^7, -SR^7, -S(O)R^{10}, -S$(O)_2R^{10}$, -NR^7R^8, protected -OH, -N(R^8)C(O)R^7, -OC(O)NR^7R^8, -N(R^8)C(O)NR^7R^8, -P(O)$(OR^7)_2$, -SO_2NR^7R^8, -SO_3H, or -N(R^8)SO_2R^{10},

where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -NR^8R^9, cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -CONR^8R^9, -$CONH_2$, aryl, heteroaryl, heterocycloalkyl, -C(O)aryl, -C(O)heterocycloalkyl, and -C(O)heteroaryl, where said aryl, heteroaryl, heterocycloalkyl, aryl, -C(O)aryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano and nitro,

or said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl) and -$CONH_2$;

R^6 is hydrogen, halogen, C_1-C_4 alkyl, or -OR^7;

or R^3 and R^4 or R^4 and R^5 or R^5 and R^6 taken together are alkylenedioxy;

X is O or S;

Y is -OH or -SH;

Z is hydrogen or C_1-C_4 alkyl;

wherein each R^7 is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl, -C_2-C_6 alkenyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl-heterocycloalkyl, -C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^9, -NR^8R^9, cyano, nitro, -CO_2R^9, -$CONR^8R^9$, -$NR^8CONR^8R^9$, -$OCONR^8R^9$, -$SO_2NR^8R^9$, and -COR^9,

or any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OR^9, -NR^8R^9, cyano, nitro, -CO_2R^9, -$CONR^8R^9$, -$NR^8CONR^8R^9$, -$OCONR^8R^9$, -$SO_2NR^8R^9$, and -COR^9;

each R^8 is independently selected from hydrogen and C_1-C_6 alkyl;

each R^9 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_4 alkyl-C_3-C_8 cycloalkyl, -C_1-C_4 alkyl-heterocycloalkyl, -C_1-C_4 alkyl-aryl, or -C_1-C_4 alkyl-heteroaryl

where said cycloalkyl, heterocycloalkyl, aryl , heteroaryl, -alkylcycloalkyl, -alkylheterocycloalkyl, -alkylaryl or -alkylheteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, cyano, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2C_1-C_6 alkyl, -CO_2H, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), and -$CONH_2$;

or, when present in any NR^7R^8 or NR^8R^9, each R^7 and R^8 or each R^8 and R^9, independently, taken together with the nitrogen to which they are attached represent a 3-6-membered saturated ring optionally containing one other heteroatom selected from oxygen and nitrogen, where said 3-6-membered ring is unsubstituted or substituted with one or more substituents independently selected from hydrogen, C_1-C_6 alkyl, halogen, cyano, -OC_1-C_6 alkyl, -OH, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2H, -C(O)OC_1-C_6 alkyl, -C(O)C_1-C_6 alkyl, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), -$CONH_2$,

C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl-C_1-C_6 alkyl-, heterocycloalkyl-C_1-C_6 alkyl-, aryl-C_1-C_6 alkyl- and heteroaryl-C_1-C_6 alkyl-, and where said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl-, heterocycloalkylalkyl-, arylalkyl- or heteroarylalkyl- is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, cyano, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2C_1-C_6 alkyl, -CO_2H, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), and -$CONH_2$;

each R^{10} is independently selected from the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl, -C_2-C_6 alkenyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl-heterocycloalkyl, -C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^{11}, -NR^8R^{11}, cyano, nitro, -CO_2R^{11}, -$CONR^8R^{11}$, -$NR^8CONR^8R^{11}$, -$OCONR^8R^{11}$, -$SO_2NR^8R^{11}$, and -COR^{11},

and where any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OR^{11}, -NR^8R^{11}, cyano, nitro, -CO_2R^{11}, -$CONR^8R^{11}$, -$NR^8CONR^8R^{11}$, -$OCONR^8R^{11}$, -$SO_2NR^8R^{11}$, and -COR^{11};

each R^{11} is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

This invention is also directed to a prodrug of a compound according to Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof. In addition, this invention is directed to pharmaceutical compositions comprising a compound according to Formula I, or a tautomer thereof, or a prodrug thereof, or salts or solvates thereof.

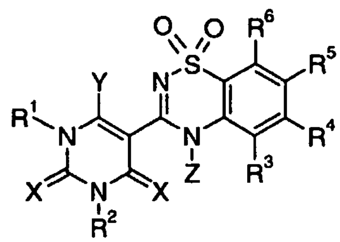
In another embodiment, this invention is directed to a method of inhibiting an RNA-containing virus comprising contacting the virus with an effective amount of a compound of Formula I. In yet another embodiment, this invention is directed to a method of treating infection or disease caused by an RNA-containing virus which comprises administering to a

subject in need thereof, an effective amount of a compound according to Formula I. This invention is particularly directed to methods of inhibiting hepatitis C virus. This invention is also directed to a method for inhibiting replication of hepatitis C virus which comprises inhibiting replication of both positive and negative strand HCV-RNA.

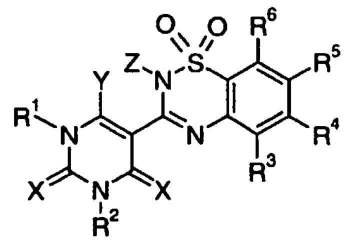
In yet another embodiment, this invention is directed to the use of a compound of Formula I, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of an RNA-containing virus. Particularly, this invention is directed to the use of a compound of Formula I, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits hepatitis C virus. More particularly, this invention is directed to the use of a compound of Formula I, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits replication of both positive and negative strand HCV-RNA.

DETAILED DESCRIPTION OF THE INVENTION

It will be appreciated by those skilled in the art that the compounds of this invention, represented by generic Formula I, above, exist in tautomeric forms having Formula I-A and Formula I-B, as follows:

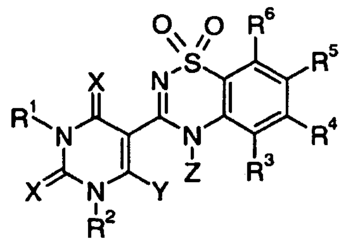


I-A

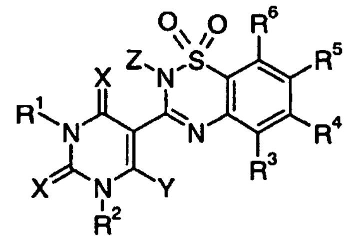


I-B

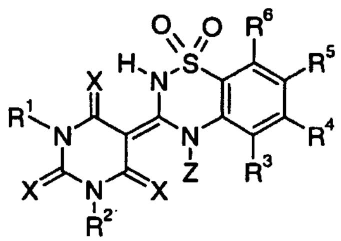
In addition, it will be appreciated by those skilled in the art, that the compounds of this invention may exist in several other tautomeric forms. All tautomeric forms of the compounds described herein are intended to be encompassed within the scope of the present invention. Examples of some of the other possible tautomeric forms of the compounds of this invention include, but are not limited to:



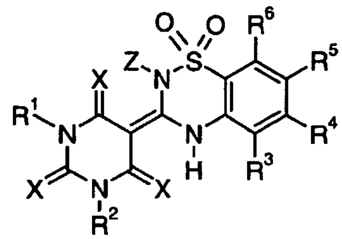
I-C



I-D



I-I



I-J

As a convention, the compounds exemplified herein have been assigned names based on the structure of the tautomer of Formula I-A. It is to be understood that any reference to such named compounds is intended to encompass all tautomers of the named compounds and any mixtures of tautomers of the named compounds.

As used herein, the term "alkyl" represents a straight-or branched-chain saturated hydrocarbon, which may be unsubstituted or substituted by one, or more of the substituents defined herein. Exemplary alkyls include, but are not limited to methyl (Me), ethyl (Et), propyl, isopropyl, butyl, isobutyl, t-butyl and pentyl. The term "lower alkyl" refers to an alkyl containing from 1 to 4 carbon atoms.

When the term "alkyl" (or alkenyl or alkynyl) is used in combination with other substituent groups, such as "haloalkyl" or "arylalkyl", the term "alkyl" is intended to encompass a divalent straight or branched-chain hydrocarbon radical. For example, "cycloalkylalkyl" is intended to mean the radical -alkyl-cycloalkyl, wherein the alkyl moiety thereof is a divalent straight or branched-chain hydrocarbon radical and the cycloalkyl moiety thereof is as defined herein, and is represented by the bonding arrangement present in the groups $-CH_2$-cyclopropyl, $-CH_2$-cyclohexyl, or $-CH_2(CH_3)CHCH_2$-cyclopentenyl. "Arylalkyl" is intended to mean the radical –alkylaryl, wherein the alkyl moiety thereof is a divalent straight or branched-chain carbon radical and the aryl moiety thereof is as defined herein, and is represented by the bonding arrangement present in a benzyl group ($-CH_2$-phenyl).

As used herein, the term "alkenyl" represents a straight-or branched-chain hydrocarbon containing one or more carbon-carbon double bonds. An alkenyl may be unsubstituted or substituted by one or more of the substituents defined herein. Exemplary alkenyls include, but are not limited ethenyl, propenyl, butenyl, isobutenyl and pentenyl.

As used herein, the term "alkynyl" represents a straight-or branched-chain hydrocarbon containing one or more carbon-carbon triple bonds and, optionally, one or more carbon-carbon double bonds. An alkynyl may be unsubstituted or substituted by one or more of the substituents defined herein. Exemplary alkynyls include, but are not limited ethynyl, butynyl, propynyl (propargyl, isopropynyl), pentynyl and hexynyl.

"Cycloalkyl" represents a group or moiety comprising a non-aromatic monocyclic, bicyclic, or tricyclic hydrocarbon containing from 3 to 14 carbon atoms which may be unsubstituted or substituted by one or more of the substituents defined herein and may be saturated or partially unsaturated. Exemplary cycloalkyls include monocyclic rings having from 3-7, preferably 3-6, carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl and cycloheptyl.

"Heterocycloalkyl" represents a group or moiety comprising a non-aromatic, monovalent monocyclic, bicyclic, or tricyclic radical, which is saturated or partially unsaturated, containing 3 to 18 ring atoms, which includes 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, and which may be unsubstituted or substituted by one or more of the substituents defined herein. Illustrative examples of heterocycloalkyls include, but are not limited to, azetidinyl, pyrrolidyl (or pyrrolidinyl), piperidinyl, piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl (or tetrahydrofuranyl), dihydrofuryl, oxazolinyl, thiazolinyl, pyrazolinyl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, azabicylo[3.2.1]octyl, azabicylo[3.3.1]nonyl, azabicylo[4.3.0]nonyl, oxabicylo[2.2.1]heptyl and 1,5,9-triazacyclododecyl. Generally, in the compounds of this invention, heterocycloalkyl is a monocyclic heterocycloalkyl, such as azetidinyl, pyrrolidyl (or pyrrolidinyl), piperidyl (or piperidinyl), piperazinyl, morpholinyl, tetrahydro-2H-1,4-thiazinyl, tetrahydrofuryl (or tetrahydrofuranyl), tetrahydrothienyl, dihydrofuryl, tetrahydropyranyl, dihydropyranyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathianyl, 1,3-dithianyl, oxazolinyl, thiazolinyl and pyrazolinyl.

"Aryl" represents a group or moiety comprising an aromatic, monovalent monocyclic or bicyclic hydrocarbon radical containing from 6 to 10 carbon ring atoms, which may be unsubstituted or substituted by one or more of the substituents defined herein, and to which may be fused one or more cycloalkyl rings, which may be unsubstituted or substituted by one

or more substituents defined herein. Generally, in the compounds of this invention, aryl is phenyl.

"Heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic, bicyclic, or tricyclic radical, containing 5 to 18 ring atoms, including 1 to 5 heteroatoms selected from nitrogen, oxygen and sulfur, which may be unsubstituted or substituted by one or more of the substituents defined herein. This term also encompasses bicyclic or tricyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, which may be unsubstituted or substituted by one or more of the substituents defined herein. Illustrative examples of heteroaryls include, but are not limited to, thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl (or furanyl), isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl (or pyridinyl), pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl, tetrazolyl, benzo[b]thienyl, naphtho[2,3-b]thianthrenyl, isobenzofuryl, 2,3-dihydrobenzofuryl, chromenyl, chromanyl, xanthenyl, phenoxathienyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthridinyl, quinzolinyl, benzothiazolyl, benzimidazolyl, tetrahydroquinolinyl, cinnolinyl, pteridinyl, carbozolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenathiazinyl, and phenoxazinyl. Generally, in the compounds of this invention, heteroaryl is a monocyclic heteroaryl, such as thienyl, pyrrolyl, imidazolyl, pyrazolyl, furyl, isothiazolyl, furazanyl, isoxazolyl, oxazolyl, oxadiazolyl, thiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrazinyl, triazolyl and tetrazolyl.

The terms "halogen" and "halo" represent chloro, fluoro, bromo or iodo substituents. "Hydroxy" is intended to mean the radical –OH. "Alkoxy" is intended to mean the radical $-OR_a$, where R_a is an optionally substituted alkyl group. Exemplary alkoxy include methoxy, ethoxy, propoxy, and the like. "Lower alkoxy" groups have optionally substituted alkyl moieties from 1 to 4 carbons. "Alkylenedioxy" is intended to mean the divalent radical $-OR_aO-$ which is bonded to adjacent atoms (e.g., adjacent atoms on a phenyl or naphthyl ring), wherein R_a is a C_1-C_2 alkyl group. Exemplary alkylenedioxy-substituted phenyls include benzo[1,3]dioxyl and 2,3-dihydro-benzo[1,4]dioxyl.

In one embodiment of the compounds of this invention, R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, carboxy-C_1-C_4 alkyl, unsubstituted aryl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and cyano.

In other embodiments of this invention, R^1 is H, $-CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, $-(CH_2)_2CH(CH_3)_2$, $-CH_2CO_2H$, $-(CH_2)_3CO_2H$, $-CH_2CH(CH_3)_2$, -phenyl, $-CH_2$(phenyl), (4-OCH_3-phenyl)CH_2-, and (2-CN-phenyl)CH_2-.

In yet another embodiment, R^2 is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, -(C_1-C_2 alkyl)-(C_3-C_6 cycloalkyl), -(C_1 alkyl)-heterocycloalkyl, -(C_1 alkyl)-aryl, or -(C_1 alkyl)-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -OCH_3, -SCH_3, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-aryl, or -(C_1-C_4 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from -CH_3, halogen, nitro, cyano, -OH, -O(C_1-C_4 alkyl), -NH_2, -NH(C_1-C_4 alkyl) and -N(C_1-C_4 alkyl)(C_1-C_4 alkyl).

In yet another embodiment, R^2 is C_2-C_6 alkyl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, and cyano.

In specific embodiments, R^2 is -$(CH_2)_2CH(CH_3)_2$, -$(CH_2)_3CH_3$, or -CH_2(phenyl).

In another embodiment, R^3 is H, halogen, C_1-C_4 alkyl, -OCH_3 or -OH. In specific embodiments, R^3 may be H, -CH_3, -OCH_3 or -OH.

In one other embodiment, R^4 is H, halogen, -OCH or -OH. In specific embodiments, R^4 may be H, Br, -OH, or -OCH_3.

In one embodiment of this invention, R^5 is hydrogen, halogen, C_1-C_2 alkyl, C_2 alkenyl, -C(O)OR^a, -C(O)R^a, -OR^b, -NR^aR^d, -C(O)NR^aR^d, where said alkyl or alkenyl is unsubstituted or substituted with a substituent selected from -NH_2, -$CONH_2$ and 5-6 membered heterocycloalkyl or heteroaryl, R^a is H or methyl, R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -NH_2, -CO_2H, -$CONH_2$, -C(O)OC_1-C_2 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, -NH_2, and -$CONH_2$, R^d is H or C_1-C_2 alkyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl, or R^a and R^d taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycloalkyl ring, which optionally contains an additional nitrogen heteroatom and which is unsubstituted or substituted with -C(O)C_1-C_2 alkyl.

In another embodiment, R^6 is hydrogen, halogen, C_1-C_4 alkyl or -$OR^{b'}$, where $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -NH_2, -CO_2H, -$CONH_2$, -C(O)OC_1-C_2 alkyl,

-CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -CONH(C_1-C_4 alkyl). In another embodiment, R^6 is hydrogen or halogen.

In yet another embodiment, R^3 and R^4 or R^4 and R^5 or R^5 and R^6 taken together are alkylenedioxy.

In specific embodiments, R^3, R^4, R^5, and R^6 are each H.

Preferably, in the compounds of this invention, X is O, Y is OH.

In another embodiment of the compounds of this invention, Z is H or methyl. In specific embodiments, Z is H.

It is to be understood that this invention encompasses all combinations of particular, specific and.or preferred embodiments described herein.

Accordingly, one embodiment of this invention comprises compounds wherein: R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, carboxy-C_1-C_4 alkyl, unsubstituted aryl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and cyano; R^2 is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, -(C_1-C_2 alkyl)-(C_3-C_6 cycloalkyl), -(C_1 alkyl)-heterocycloalkyl, -(C_1 alkyl)-aryl, or -(C_1 alkyl)-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OCH_3$, $-SCH_3$, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-aryl, or -(C_1-C_4 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from $-CH_3$, halogen, nitro, cyano, -OH, -O(C_1-C_4 alkyl), $-NH_2$, -NH(C_1-C_4 alkyl) and -N(C_1-C_4 alkyl)(C_1-C_4 alkyl); R^3 is H, halogen, C_1-C_4 alkyl, $-OCH_3$ or -OH; R^4 is H, halogen, $-OCH_3$ or -OH; R^5 is hydrogen, halogen, C_1-C_2 alkyl, C_2 alkenyl, $-C(O)OR^a$, $-C(O)R^a$, $-OR^b$, $-NR^aR^d$, $-C(O)NR^aR^d$, where said alkyl or alkenyl is unsubstituted or substituted with a substituent selected from $-NH_2$ and $-CONH_2$, R^a is H or methyl, R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, -C(O)OC_1-C_2 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, R^d is H or C_1-C_2 alkyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl, or R^a and R^d taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycloalkyl ring, which optionally contains an

additional nitrogen heteroatom and which is unsubstituted or substituted with -C(O)C_1-C_2 alkyl, R^6 is hydrogen, halogen, C_1-C_4 alkyl or -$OR^{b'}$, where $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -NH_2, -CO_2H, -$CONH_2$, -C(O)OC_1-C_2 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -CONH(C_1-C_4 alkyl); X is O; Y is OH; and Z is H or methyl.

In another embodiment of the compounds of this invention, R^1 hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, carboxy-C_1-C_4 alkyl, unsubstituted aryl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and cyano; R^2 is C_2-C_6 alkyl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, and cyano; R^3, R^4, R^5, and R^6 are each H; X is O; Y is OH and Z is H.

In yet another embodiment of the compounds of this invention, R^1 is H, -CH_3, -CH_2CF_3, -$CH(CH_3)_2$, -$(CH_2)_3CH_3$, -$(CH_2)_2CH(CH_3)_2$, -CH_2CO_2H, -$(CH_2)_3CO_2H$, -$CH_2CH(CH_3)_2$, -phenyl, -CH_2(phenyl), (4-OCH_3-phenyl)CH_2-, and (2-CN-phenyl)CH_2-; R^2 is -$(CH_2)_2CH(CH_3)_2$, -$(CH_2)_3CH_3$, or -CH_2(phenyl); R^3, R^4, R^5, and R^6 are each H; X is O; Y is OH; and Z is H.

If a substituent described herein is not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, *Protecting Groups in Chemical Synthesis* (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful as an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

In the compounds of this invention, various substituents may be a "protected -OH" group. This term refers to a substituent represented as -OR^P, where R^P refers to a suitable protecting group for an -OH moiety. Hydroxyl protecting groups are well known in the art and any hydroxyl protecting group that is useful in the methods of preparing the compounds of this

invention may be used. Exemplary hydroxyl protecting groups include benzyl, tetrahydropyranyl, silyl (trialkyl-silyl, diaryl-alkyl-silyl, etc.) and various carbonyl-containing protecting groups, as disclosed in T. Greene and P. Wuts, *supra*. For example, in the compounds of this invention, R^2 may be the protected hydroxyl moiety -OSi(*tert*-butyl)(CH_3)$_2$.

The compounds of this invention may contain at least one chiral center and may exist as single stereoisomers (e.g., single enantiomers), mixtures of stereoisomers (e.g. any mixture or enantiomers or diastereomers) or racemic mixtures thereof. All such single stereoisomers, mixtures and racemates are intended to be encompassed within the broad scope of the present invention. Compounds identified herein as single stereoisomers are meant to describe compounds that are present in a form that are at least 90% enantiomerically pure. Where the stereochemistry of the chiral carbons present in the chemical structures illustrated herein is not specified, the chemical structure is intended to encompass compounds containing either stereoisomer of each chiral center present in the compound. Such compounds may be obtained synthetically, according to the procedures described herein using optically pure (enantiomerically pure) or substantially optically pure materials. Alternatively, these compounds may be obtained by resolution/separation of a mixture of stereoisomers, including racemic mixtures, using conventional procedures. Exemplary methods that may be useful for the resolution/separation of mixtures of stereoisomers include chromatography and crystallization/re-crystallization. Other useful methods may be found in "*Enantiomers, Racemates, and Resolutions,*" J. Jacques et al., 1981, John Wiley and Sons, New York, NY, the disclosure of which is incorporated herein by reference.

The compounds of this invention may possess one or more unsaturated carbon-carbon double bonds. All double bond isomers, both the cis (Z) and trans (E) isomers, and mixtures thereof are intended to be encompassed within the scope of the present invention.

The term "pharmaceutically acceptable salt" is intended to describe a salt that retains the biological effectiveness of the free acid or base of a specified compound and is not biologically or otherwise undesirable.

If an inventive compound is a base, a desired salt may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid,

methanesulfonic acid, ethanesulfonic acid or the like. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, phenylacetates, phenylpropionates, phenylbutrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates mandelates, and sulfonates, such as xylenesulfonates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates and naphthalene-2-sulfonates.

If an inventive compound is an acid, a desired salt may be prepared by any suitable method known to the art, including treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary), an alkali metal or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as ethylene diamine, dicyclohexylamine, ethanolamine, piperidine, morpholine, and piperazine, as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium. Particular pharmaceutically acceptable salts of a compound of Formula I include the sodium salt and the potassium salt.

Because the compounds of this invention may contain both acid and base moieties, pharmaceutically acceptable salts may be prepared by treating these compounds with an alkaline reagent or an acid reagent, respectively. Accordingly, this invention also provides for the conversion of one pharmaceutically acceptable salt of a compound of this invention, e.g., a hydrochloride salt, into another pharmaceutically acceptable salt of a compound of this invention, e.g., a sodium salt.

The term "solvate" is intended to mean a pharmaceutically acceptable solvate form of a specified compound that retains the biological effectiveness of such compound. Examples of solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine. In the case of compounds, salts, or solvates that are solids, it is understood by those skilled in the art that the inventive compounds, salts, or solvates may exist in different crystal forms, all of which are intended to be within the scope of the present invention and specified formulas.

Also included within the scope of this invention are prodrugs of the compounds of this invention. The term "prodrug" is intended to mean a compound that is converted under physiological conditions, e.g., by solvolysis or metabolically, to a compound of Formula I, or a

tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof. A prodrug may be a derivative of one of the compounds of this invention that contains, for example, a carboxylic acid ester or amide moiety or an enol-ester moiety that may be cleaved under physiological conditions. A prodrug containing such a moiety may be prepared according to conventional procedures, for example, by treatment of a compound of Formula I, containing an amino, amido or hydroxyl moiety with a suitable derivatizing agent, for example, a carboxylic acid halide or acid anhydride, or by converting a compound of Formula I, containing a carboxyl moiety to an ester or amide or by converting a compound of Formula I, containing a carboxylic acid ester moiety to an enol-ester. Prodrugs of the compounds of this invention may be determined using techniques known in the art, for example, through metabolic studies. See, e.g., "Design of Prodrugs," (H. Bundgaard, Ed.) 1985, Elsevier Publishers B.V., Amsterdam, The Netherlands.

The present invention is directed to a method of inhibiting an RNA-containing virus which comprises contacting the virus with an effective amount of a compound of Formula I. This invention is also directed to a method of treating infection or disease caused by an RNA-containing virus comprising administering to a subject in need thereof, an effective amount of the compound of Formula I. Specifically, this invention is directed to a method of inhibiting HCV activity, comprising contacting the virus with an effective amount of a compound of Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof. For example, HCV activity may be inhibited in mammalian tissue by administering to a subject in need thereof a compound of Formula I or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

A therapeutically "effective amount" is intended to mean that amount of a compound that, when administered to a mammal in need of such treatment, is sufficient to effect treatment, as defined herein. Thus, e.g., a therapeutically effective amount of a compound of Formula I or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof is a quantity of an inventive agent that, when administered to a mammal in need thereof, is sufficient to modulate or inhibit the activity of HCV such that a disease condition which is mediated by that activity is reduced, alleviated or prevented. The amount of a given compound that will correspond to such an amount will vary depending upon factors such as the particular compound (e.g., the potency (IC_{50}), efficacy (EC_{50}), and the biological half-life of the particular compound), disease condition and its severity, the identity (e.g., age, size and weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. Likewise, the duration of treatment and the time period of administration (time period between dosages and the timing of the dosages, e.g., before/with/after meals) of the compound

will vary according to the identity of the mammal in need of treatment (e.g., weight), the particular compound and its properties (e.g., pharmaceutical characteristics), disease or condition and its severity and the specific composition and method being used, but can nevertheless be determined by one of skill in the art.

In addition, this invention is directed to a method for inhibiting replication of hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, which method comprises contacting a cell infected with said virus with an effective amount of a compound of Formula I. This invention is also directed to a method of treating infection or disease caused by hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, which method comprises administering to a subject in need thereof, an effective amount of a compound of Formula I. More specifically, this invention is directed to a method of inhibiting replication of both positive and negative strand HCV-RNA with a compound of Formula I, wherein the compounds demonstrate substantially equal inhibition of positive strand HCV-RNA replication and negative strand HCV-RNA replication. That is, for a given compound of this invention, the IC_{50} for inhibition of positive strand HCV-RNA replication is not statistically different (less than a 2-fold difference) from the IC_{50} for inhibition of negative strand HCV-RNA replication. Generally, the compounds of this invention demonstrate an IC_{50} for inhibition of positive strand HCV-RNA replication that is $\pm 30\%$ the IC_{50} for inhibition of negative strand HCV-RNA replication.

"Treating" or "treatment" is intended to mean at least the mitigation of a disease condition (acute, chronic, latent, etc.) in a subject (a mammal, such as a human), where the disease condition is caused by an infectious RNA-containing virus. The methods of treatment for mitigation of a disease condition include the use of the compounds in this invention in any conventionally acceptable manner, for example for prevention, retardation, prophylaxis, therapy or cure of a disease. The compounds of Formula I, Formula II and Formula III of this invention are particularly useful for the treatment of acute, chronic or latent HCV diseases, such as acute and chronic hepatitis infection, hepatocellular carcinoma, liver fibrosis, or other HCV-related diseases. The compounds of Formula I, Formula II and Formula III of this invention may also be useful for treatment of diseases caused by infectious RNA-containing viruses other than HCV, including, but not limited to, Dengue, HIV or picornaviruses. Chronic fatigue syndrome is another disease that may be treatable using the compounds of this invention.

An inventive compound of Formula I, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof may be administered to a subject as a pharmaceutical composition in any pharmaceutical form that is recognizable to the skilled artisan as being

suitable. Suitable pharmaceutical forms include solid, semisolid, liquid, or lyophilized formulations, such as tablets, powders, capsules, suppositories, suspensions, liposomes, and aerosols. Pharmaceutical compositions of the invention may also include suitable excipients, diluents, vehicles, and carriers, as well as other pharmaceutically active agents, depending upon the intended use or mode of administration. Administration of a compound of the Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof, may be performed according to any of the generally accepted modes of administration available to those skilled in the art. The compounds of this invention may be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops. Alternatively, injection (e.g., parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. The compounds of the invention may also be formulated in liposome-containing preparations, particularly liposome-containing preparations useful for delivery of the compounds of this invention to the liver or potentially to nonhepatic reservoirs of infection. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories. For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

Compositions containing a compound of Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof, which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing

solid formulations may be used. Examples of such carriers include starch, calcium sulfate dihydrate, magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule, any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and may be incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof, which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is formulated and administered in a unit dosage form. For oral application, for example, one or more tablets or capsules may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. A dose of the pharmaceutical composition contains at least a therapeutically effective amount of the active compound (i.e., a compound of Formula I, or a tautomer thereof, or pharmaceutically acceptable salt or solvate thereof). The selected dose may be administered to a mammal, for example, a human patient, in need of treatment mediated by inhibition of HCV activity by any known or suitable method of administering the dose, including: topically, for example, as an ointment, or cream, orally, rectally, for example, as a suppository, parenterally by injection, or continuously by intravaginal, intranasal, intrabronchial, intraaural, or intraocular infusion.

Treatment of all forms of infection or disease (acute, chronic, latent etc) or as prophylaxis with these compounds (or their salts etc.) may be achieved using the compounds of this invention as a monotherapy, in dual or multiple combination therapy, such as in combination with other antivirals, in combination with an interferon, in combination with an interferon and ribavirin or levovirin, or in combination with one or more agents which include but are not limited to: immunomodulatory agents (such as cytokines, suppressors of cytokines and/or cytokine signalling, or immune modifiers, adjuvants and the like), immunomodulatory agents that enhance the body's immune system (such as vitamins, nutritional supplements, antioxidant compositions, vaccines or immunostimulating complexes, such as vaccines comprising a multimeric presentation of an antigen and adjuvant), other direct antiviral agents, indirect antiviral agents or agents which target viral RNA and impair translation or replication or modulate signalling or cellular host factors, or host-viral interface, immunoglobulins, antisense agents against HCV, peptide-nucleic acid conjugates, oligonucleotides, ribozymes, polynucleotides, anti-inflammatory agents, pro-inflammatory agents, antibiotics, hepatoprotectants, or any anti-infectious agents and the like, or combinations thereof. Moreover, the additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively, these additional agents may be separately administered as part of a multiple dosage form. As used herein the term "an interferon" is intended to mean any form of interferon, which includes, but is not limited to, natural or recombinant forms of alpha, beta or gamma interferons, albumin-linked interferons, or pegylated interferons.

Representative compounds of this invention include the compounds of Examples 1-16 or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

Compounds of the present invention include:

3-butyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione,

1,3-dibutyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-propyl-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1,3-bis-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1-(3-carboxypropyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-phenyl-1*H*-pyrimidine-2,4-dione,

1-benzyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H* –pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-(4-methoxybenzyl)-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1,3-dibenzyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1-carboxymethyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1-(2-cyanobenzyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2-methylpropyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-isopropyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-methyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, and

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrimidine-2,4-dione,

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

Preferred compounds of this invetion include 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1,3-bis-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-(4-methoxybenzyl)-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2-methylpropyl)-1*H*-pyrimidine-2,4-dione, and 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-isopropyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, or a salt or solvate thereof.

The following compounds did not demonstrate biological activity at the screening rate of 10 uM, however, such compounds may demonstrate activity at higher testing rates or when evaluated under different assay conditions: 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(4-chloro-phenyl)-1*H*-pyrimidine-2,4-dione, 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(3-carboxy-phenyl)-

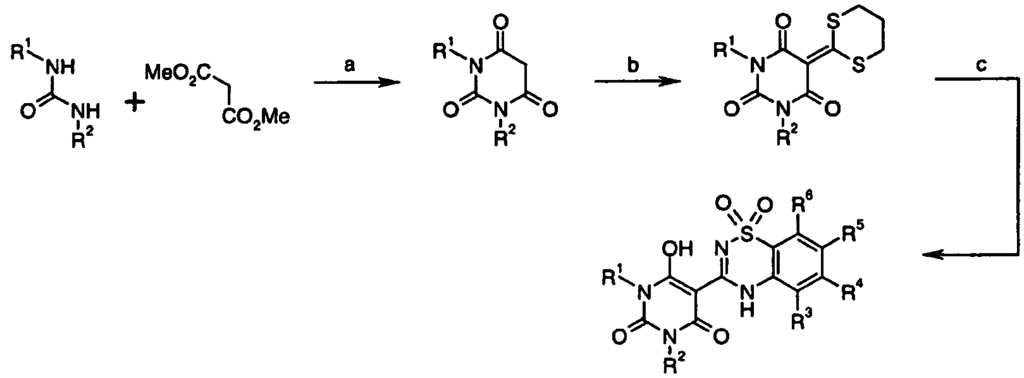
1*H*-pyrimidine-2,4-dione, and 1-(2-carbamoyl-benzyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

GENERAL SYNTHETIC METHODS

This invention is also directed to methods for the synthesis of the compounds of Formula I and tautomers thereof.

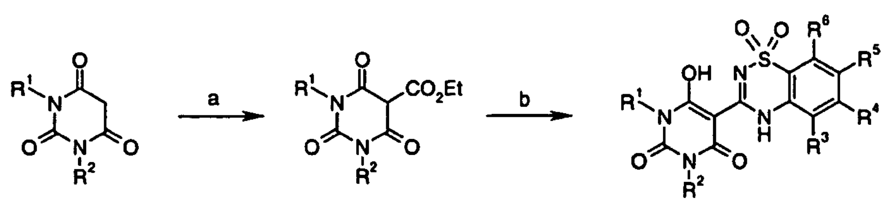
Included in this invention is a process according to Schemes 1 - 6 for the preparation of the compounds of Formula I:

Scheme 1



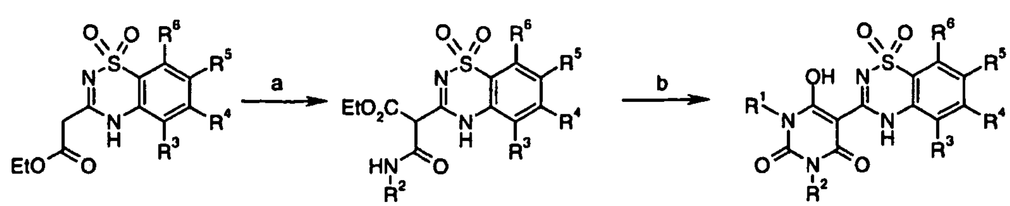
Conditions: a) NaOMe, MeOH, reflux; b) 1. CS_2, Et_3N, DMSO, 2. $I(CH_2)_3I$; c) 1. 2-$NH_2ArSO_2NH_2$, $AlMe_3$, dioxane, reflux, 2. aq NaOH, reflux, then aq HCl

Scheme 2



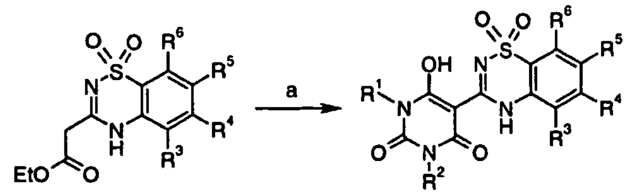
Conditions: a) Ethyl chloroformate, pyridine, RT; b) 1. 2-$NH_2ArSO_2NH_2$, PhMe, reflux; 2. $POCl_3$, reflux; 3. NaOH aq MeOH, reflux, then aq HCl

Scheme 3



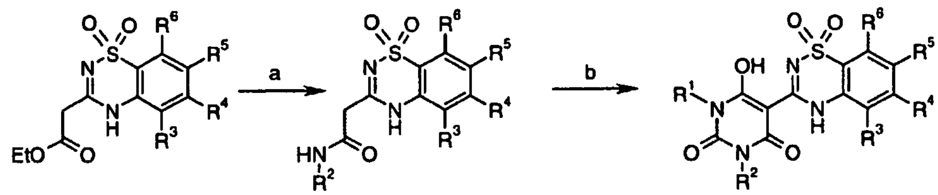
Conditions: a) R^2NCO, Et_3N, CH_2Cl_2, reflux; b) NaH, R^1NCO, THF or dioxane, reflux

Scheme 4 (where $R^1 = R^2$)



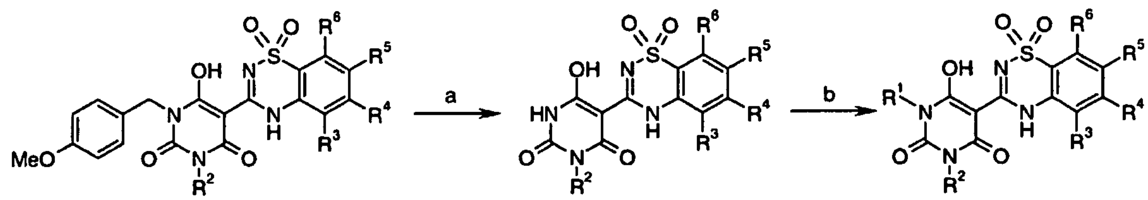
Conditions: a) NaH, RNCO, THF or dioxane, reflux

Scheme 5



Conditions: a) R^2NH_2, PhMe, reflux; b) NaH, R^1NCO, dioxane, reflux

Scheme 6



Conditions: a) H_2SO_4, H_2O; b) NaH or K_2CO_3, R^1Hal, DMF, 100 °C

Also included within the scope of the present invention are intermediate compounds that are useful for the preparation of the compounds of Formula I. Such useful intermediate compounds include:± ethyl 2-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-3-(3-methylbutylamino)-3-oxopropionate

The activity of the inventive compounds as inhibitors of HCV activity may be measured by any of the suitable methods known to those skilled in the art, including *in vivo* and *in vitro* assays. For example, the HCV NS5B inhibitory activity of the compounds of Formula I was determined using standard assay procedures described in Behrens et al., EMBO J. 15:12-22 (1996), Lohmann et al., Virology 249:108-118 (1998) and Ranjith-Kumar et al., J. Virology 75:8615-8623 (2001). Unless otherwise noted, the compounds of this invention have demonstrated *in vitro* HCV NS5B inhibitory activity in such standard assays and have IC_{50}'s in

the range of 0.0001 μM to 100 μM. Representative compounds of Formula I, Examples 1-16 have all demonstrated *in vitro* HCV NS5B inhibitory activity and have IC_{50}'s in the range of 0.2 μM to 20 μM. Recently, cell-based replicon systems for HCV have been developed, in which the nonstructural proteins stably replicate subgenomic viral RNA in Huh7 cells (Lohmann et al., Science (1999) and Blight et al., Science (2000). In the absence of a purified, functional HCV replicase consisting of viral non-structural and host proteins, our understanding of *Flaviviridae* RNA synthesis comes from studies using active recombinant RdRps and validation of these studies in the HCV replicon system. Inhibition of recombinant purified HCV polymerase with compounds in *in vitro* biochemical assays may be validated using the replicon system whereby the polymerase exists within a replicase complex, associated with other viral and cellular polypeptides in appropriate stoichiometry. Demonstration of cell-based inhibition of HCV replication may be more predictive of *in vivo* function than demonstration of HCV NS5B inhibitory activity in *in vitro* biochemical assays.

Advantageously, the compounds of this invention inhibit both positive and negative strand HCV-RNA replication. The following methods have been developed and used for determining the positive and negative strand HCV-RNA replication inhibition activity of the compounds of this invention.

Test Method 1

Method for positive strand replicon HCV-RNA detection in replicon cells

Replicon cells were plated at 3 X 10^3 cells per well in a 96-well plate plates at 37° and 5% CO_2 in DMEM (Dulbecco's Minimal Essential Medium) containing 10% FCS (fetal calf serum), 1% NEAA (nonessential amino acids) and 1 mg/ml Geneticin (G418 neomycin). After allowing 4 h for cell attachment, 1 μl of a solution of candidate antiviral agent was added to the medium (n = 8 wells per dilution). Briefly, eleven 2.5-fold dilutions of 1 mM stock test compound in DMSO (dimethylsulfoxide) were prepared with final concentration ranging from 10000 nM to 1.0 nM. Plates were incubated for 40 h, until reaching 80% confluence. After removal of medium, 150 μl Buffer RLT (Qiagen, Valencia, California, US) was added to each well and RNA purified according to manufacturer's recommendations (Qiagen RNAeasy) and were eluted twice in 45 μl dH_2O prior to RT-PCR. Approximately 40 μl of TaqMan EZ RT-PCR (Applied Biosystems, Foster City, California, US) master mix (1X TaqMan EZ Buffer, 3 mM $Mn(OAc)_2$, 0.3 mM dATP, 0.3 mM dCTP, 0.3 mM dGTP, 0.6 mM dUTP, 0.2 mM neo-forward, 0.2 mM neo-reverse, 0.1 mM neo-probe, 1X Cyclophilin Mix, 0.1 Unit/μl r*Tth* DNA Polymerase, 0.01 Unit/μl AmpErase UNG, and H_2O to 40 μl) was added to each tube of 96-tube optical plate along with 10 μl of RNA elution. Primers and probes specific for the positive strand RNA detection of neomycin gene were: neo-

forward: 5'CCGGCTACCTGCCCATTC3' (SEQ ID NO 1); neo-reverse: 5'CCAGATCATCCTGATCGACAAG3' (SEQ ID NO 2); neo-probe: 5'FAM-ACATCGCATCGAGCGAGCACGTAC-TAMRA3' (SEQ ID NO 3). For negative strand RNA detection, the cDNA primer used was 5'ACA TGC GCG GCA TCT AGA CCG GCT ACC TGC CCA TTC3' (SEQ ID NO 4) whereby the first 18 bases represent SEQ ID NO 5 linked to neo sequences; neo-forward tag: 5'ACA TGC GCG GCA TCT AGA3' (SEQ ID NO 5); neo reverse 5'CCAGATCATCCTGATCGACAAG3' (SEQ ID NO 6); neo probe: 5'FAM-ACA TCG CAT CGA GCG AGC ACG TAC-TAMRA3' (SEQ ID NO 3). Additionally, the PDAR control reagent human cyclophilin was used for normalization. Samples were mixed briefly and placed in an ABI7700 (Applied Biosystems) at 50°C, 2 min; 60°C, 30 min; and 95°C, 5 min, with cycling parameters set to 94°C, 20 s; 55°C, 1 min for 40 cycles. The relative cDNA levels for neo and cyclophilin were determined compared to DMSO-only treated controls and the ratio of neo:cyclophilin was used for IC_{50} calculation (n = 8).

Test Method 2

Method for negative strand replicon HCV-RNA detection in replicon cells

To achieve strand-specific detection, a primer containing HCV RNA (or replicon RNA sequences such as neomycin gene) and an 18 base tag of nonrelated sequence at the 5' end was for the reverse transcription (RT) reaction, 5'ACATGCGCGGCATCTAGACCGGCTACCTGCCCATTC3' (SEQ ID NO 4). A Thermoscript-RT-PCR system (Invitrogen) was used for the RT reaction according to the manufacturer's protocol, with approximately 9 µl of the cell-harvested RNA and 1 µl of primer (10 µM) incubated with RT at 60°C for 1 h. Following that incubation, 2 µl of cDNA product containing the 5' tag was amplified for TaqMan quantification using the 48 µl of TaqMan Universal Master Mix (Applied Biosystems) as well as primers, neo-forward tag: 5'ACA TGC GCG GCA TCT AGA3' (SEQ ID NO 5); neo reverse: 5'CCAGATCATCCTGATCGACAAG3' (SEQ ID NO 6); and neo probe: 5'FAM-ACA TCG CAT CGA GCG AGC ACG TAC-TAMRA3' (SEQ ID NO 3). Samples were mixed briefly and placed in an ABI7700 (Applied Biosystems) at 50°C, 2 min; 95°C, 10 min, with cycling parameters set to 94°C, 15 s; 55°C, 1 min for 40 cycles. The negative strand copy number in each reaction was determined using linear regression analysis based on the slope and intercept generated with a negative strand copy standard curve. The negative strand copies per cell were determined by dividing the total negative strand copies per reaction by the total cells per reaction.

Through routine experimentation, including appropriate manipulation and protection of any chemical functionality, synthesis of the compounds of Formula I is accomplished by methods analogous to those above and to those described in the following Experimental section.

Example 1

3-Butyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione;

a) 1-Butylpyrimidine-2,4,6-trione;

A solution of butylurea (5.00 g, 43.0 mmol), dimethylmalonate (4.91 mL, 43.0 mmol) in methanolic sodium methoxide (2M, 25.8 mL, 51.6 mmol) was heated under reflux for 6 h, then cooled and acidified to pH 1 with 1M aqueous hydrochloric acid. Most of the methanol was removed under reduced pressure, and the resulting solid filtered off and washed with cold water to give the title compound (3.96 g, 50%) as a white solid. LCMS m/e 185 (MH^+).

b) 3-Butyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione;

Carbon disulfide (1.10 mL, 18.2 mmol) was injected into a stirred solution of 1-butylpyrimidine-2,4,6-trione (1.00 g, 5.43 mmol) and triethylamine (1.51 mL, 10.9 mmol) in dimethylsulfoxide (4 mL). After stirring 2.5 h, di-iodopropane (0.624 mL, 5.43 mmol) was injected and stirring continued for 1.5 h. Water (60 mL) was added and the solid filtered, washed with water and dried to give 1-butyl-5-(1,3-dithian-2-ylidene)pyrimidine-2,4,6-trione (1.34 g, 82%) as a yellow solid, used directly in the next step.

Trimethylaluminium (0.55 mL of a 2M toluene solution, 1.10 mmol) was injected into a stirred suspension of 1-butyl-5-(1,3-dithian-2-ylidene)pyrimidine-2,4,6-trione (0.30 g, 1.00 mmol) and 2-aminobenzenesulfonamide (0.172 g, 1.00 mmol) in dioxane (6 mL) under argon. The resulting solution was heated under reflux for 24 h, then cooled and 1M aqueous sodium hydroxide (14 mL, 14 mmol) added. The mixture was heated under reflux for 1 h, then cooled and acidified to pH 1 with 1M aqueous hydrochloric acid. The insoluble material was filtered, washed with water and diethyl ether. The material obtained was boiled in diethyl ether, then cooled, filtered and dried to give the title compound (13 mg, 4%) as a cream coloured solid. ^1H NMR (300MHz, d_6-DMSO) δ 13.63 (1H, s), 11.30 (1H, br s), 7.78 (1H, d, J = 7.9 Hz), 7.65 (1H, m), 7.46-7.37 (2H, m), 3.76 (2H, t, J = 7.4 Hz), 1.52 (2H, m), 1.30 (2H, m), 0.91 (3H, t, J = 7.3 Hz).

Example 2

1,3-Dibutyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione

a) 1,3-Dibutyl-pyrimidine-2,4,6-trione

A solution of sodium methoxide in methanol (4.63 M, 7.91 mL, 36.6 mmol) was added to a mixture of dibutyl urea (5.00 g, 29.0 mmol), dimethyl malonate (3.31 mL, 29.0 mmol) and methanol (10.0 mL) at room temperature. The reaction was stirred under reflux for 24h, cooled and diluted with 1M aqueous HCl (200 mL). After stirring 1 h, the precipitate was filtered, then dissolved in diethyl ether. The solution was washed (brine), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography (silica gel, 30-40% ethyl acetate/hexanes) gave the title compound (2.82 g, 40%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 3.81 (2H, s), 3.73 (4H, m), 1.48 (4H, m), 1.28 (4H, m), 0.89 (6H, t, J = 7.3 Hz).

b) 1,3-Dibutyl-6-hydroxy-2,4-dioxopyrimidine-5-carboxylic acid, ethyl ester

Ethyl chloroformate (0.239 mL, 2.50 mmol) was added to an ice-cooled solution of 1,3-dibutyl-pyrimidine-2,4,6-trione (0.500 g, 2.08 mmol) in pyridine (3.0 mL) and dimethylformamide (100.0 mL) under nitrogen. After stirring for 24h at room temperature, 1M aqueous HCl (40.0 mL) was added, and the product was extracted with ethyl acetate. The extracts were washed (brine), dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography (silica gel, ethyl acetate, then 10% methanol/ethyl acetate) gave the title compound (0.180 g, 29%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 4.06 (2H, q, J = 7.1 Hz), 3.73 (4H, m), 1.43 (4H, m), 1.29-1.16 (7H, m), 0.87 (6H, t, J = 7.2 Hz).

c) 1,3-Dibutyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione

A mixture of 1,3-dibutyl-6-hydroxy-2,4-dioxopyrimidine-5-carboxylic acid, ethyl ester (0.101 g, 0.323 mmol) and 2-aminobenzenesulfonamide (0.061 g, 0.354 mmol) in toluene (3.0 mL) was heated under reflux for 8 h. The solvent was removed under reduced pressure and the residue chromatographed (ethyl acetate) to give a partially purified amide. A mixture of the impure amide and phosphorus oxychloride (5.0 mL) was heated under reflux for 5 h, then cooled and poured onto ice. The solid was filtered and washed (water), then dissolved in 1M aqueous NaOH (4 mL) and methanol (1 mL) and refluxed for 2h. After cooling and acidifying (1M aqueous HCl), the solid was filtered and purified by chromatography (silica gel, ethyl acetate). The product was further triturated with ether to give the title compound (0.034 g, 25%) as a white solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.97 (1H, s), 7.64 (1H, d, J = 8.0 Hz), 7.52 (1H, m),

7.29-7.24 (2H, m), 3.79 (4H, t, J = 7.3 Hz), 1.50 (4H, m), 1.29 (4H, m), 0.91 (6H, t, J = 7.3 Hz).

Example 3

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-propyl-1*H*-pyrimidine-2,4-dione

a) ± Ethyl 2-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-3-(3-methylbutylamino)-3-oxopropionate

A solution of 3-methylbutyl isocyanate (0.260 g, 2.30 mmol) in dichloromethane (4 mL) was added to a stirred mixture of (1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)acetic acid, ethyl ester (0.268 g, 1.00 mmol) and triethylamine (1.00 mL, 17.4 mmol) and this mixture refluxed for 6h. The solution was cooled and partitioned between 1M aqueous HCl and ethyl acetate. The extracts were washed (H_2O, brine) and dried ($MgSO_4$) then evaporated under reduced pressure. Chromatography (silica gel, 50-70% ethyl acetate/hexanes) and trituration with ethyl acetate gave the title compound (0.137 g, 36%). ^1H NMR (300MHz, d_6-DMSO) δ 12.2 (1H, s), 8.37 (1H, br s), 7.80 (1H, m), 7.72 (1H, m), 7.45 (2H, m), 4.67 (1H, s), 4.18 (2H, m), 3.16 (2H, m), 1.65 (1H, m), 1.32 (2H, m); 1.22 (3H, t, J = 7.5 Hz); 0.89 (6H, d, J = 6.6 Hz).

b) 5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-propyl-1*H*-pyrimidine-2,4-dione

Sodium hydride (60% in mineral oil, 0.015 g, 0.375 mmol) was added to a stirred solution of ± ethyl 2-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-3-(3-methylbutylamino)-3-oxopropionate (0.050 g, 0.131 mmol) in dioxane (1.0 mL) under argon. After, 5 min, propyl isocyanate (0.390 mL, 4.16 mmol) was injected and the reaction was heated under reflux for 4h, then cooled. 1M aqueous HCl (10 mL) was added, and the mixture extracted with ethyl acetate. The extracts were washed (H_2O, brine), dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography (silica gel, 50-75% ethyl acetate/hexanes) and trituration with ethyl ether gave the title compound (0.034 g, 62%) as a white solid. ^1H NMR (300MHz, d_6-DMSO) δ 14.00 (1H, s), 7.64 (1H, d, J = 7.8 Hz), 7.53 (1H, m), 7.26 (2H, m), 3.79 (4H, m), 1.56 (4H, m), 1.40 (1H, m), 0.91 (9H, m).

Example 4

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1,3-bis-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

Sodium hydride (60% in mineral oil, 0.045 g, 1.13 mmol) was added to a stirred suspension of (1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)acetic acid, ethyl ester (0.100 g, 0.373 mmol) in dioxane (3.0 mL) under argon. After 5 min, 3-methylbutyl isocyanate (0.170 g, 1.34 mmol) was added, and the mixture was heated under reflux for 2h, then cooled and poured into 0.5 M aqueous HCl (35.0 mL). The solid was filtered then dissolved in ethyl acetate and ether, the solution dried ($MgSO_4$) and evaporated under reduced pressure. The solid was triturated with hot ether, filtered and dried to leave the title compound (0.048 g, 29%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.75 (1H, s), 7.76 (1H, d, J = 7.8 Hz), 7.63 (1H, m), 7.39 (2H, m), 3.83 (4H, t, J = 7.6 Hz), 1.58 (2H, m), 1.43 (4H, m), 0.92 (12H, d, *J* = 6.5 Hz).

Example 5

1-(3-Carboxypropyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

a) 1-(3-Carboethoxypropyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

The procedure of Example 3(b) was followed here, using ethyl 4-isocyanatobutyrate in the place of propylisocyanate to give the title compound (60%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.90 (1H, s), 7.64 (1H, d, J = 7.9 Hz), 7.53 (1H, m), 7.27 (2H, m), 4.05 (2H, q, J =7.3 Hz), 3.83 (4H, m), 2.29 (2H, m), 1.8 (2H, m), 1.55 (1H, m), 1.41 (2H, m), 1.20 (3H, d, J = 7.5 Hz), 0.91 (6H, d, J = 6.6 Hz).

b) 1-(3-Carboxypropyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

1M aqueous NaOH (1.5 mL, 1.5 mmol) was added dropwise to a stirred solution of 1-(3-carboethoxypropyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione (0.076 g, 0.154 mmol) in methanol (6.0 mL). After stirring at room temperature for 2h, 0.2M aqueous HCl (30 mL) was added and the product was extracted with ethyl acetate. The extracts were washed (brine), dried ($MgSO_4$) and evaporated under reduced pressure. After flash chromatography (0-5% methanol/ethyl acetate with 0.5% acetic acid) the product was triturated with ethyl ether, filtered and dried. The material was

further purified by reverse phase HPLC (CombiPrep ODS-A, 10-90% acetonitrile/water + 0.1% trifluoroacetic acid), then reprecipitated from solution in aqueous NaOH with aqueous HCl. The solid was filtered, washed (water) and dried to leave the title compound (0.009 g, 7%) as a pale yellow solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.80 (1H, s), 7.75 (1H, m), 7.63 (1H, m), 7.39 (2H, m), 3.85 (4H, m), 2.25 (2H, t, J = 7.4 Hz), 1.80 (2H, m), 1.57 (1H, m), 1.43 (2H, m), 0.93 (6H, d, J = 6.5 Hz).

Example 6

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-phenyl-1*H*-pyrimidine-2,4-dione

a) 2-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-N-(3-methylbutyl)acetamide

A mixture of (1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)acetic acid, ethyl ester (3.00 g, 11.2 mmol) and 3-methylbutylamine (1.10 g, 12.7 mmol) in toluene (20.0 mL) was heated under reflux for 3h. After cooling, the solid was filtered, washed (toluene, ether) and dried to give the title compound (3.07 g, 89%) as a yellow solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 11.90 (1H, s), 7.93 (1H, dd, J = 8.0, 1.4 Hz), 7.60 (1H, m), 7.44 (1H, m), 7.18 (1H, m), 6.84 (1H, br s), 3.68 (2H, s), 3.35 (2H, m), 1.59 (1H, m), 1.48 (2H, m), 0.93 (6H, d, J = 6.5 Hz).

b) 5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-phenyl-1*H*-pyrimidine-2,4-dione

Sodium hydride (0.100 g of a 60% oil suspension, 2.50 mmol) was added to a stirred suspension of 2-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-N-(3-methylbutyl)acetamide (0.155 g, 0.500 mmol) in dioxane (5 mL) at room temperature under argon. After 5 min, phenyl isocyanate (0.272 mL, 2.50 mmol) was injected and the mixture heated under reflux for 2 h, then cooled. 0.1M aqueous HCl (30 mL) was added and the mixture extracted with ethyl acetate. The extracts were washed (water, brine), dried ($MgSO_4$), evaporated under reduced pressure and the residue chromatographed (silica gel, 50% then 100% ethyl acetate/hexanes). The partially purified product was boiled in ethyl acetate/ether (1:1, 10 mL), cooled and the solid filtered and dried to give the title compound (0.026 g, 11%) as a cream powder. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.80 (1H, s), 7.63 (1H, d, J = 7.9 Hz), 7.53-7.34 (4H, m), 7.29-7.19 (4H, m), 3.83 (2H, t, J = 7.5 Hz), 1.59 (1H, m), 1.44 (2H, m), 0.93 (6H, d, J =6.5 Hz).

Example 7

1-Benzyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H* –pyrimidine-2,4-dione

The procedure of Example 3(b) was followed here, using benzyl in the place of propyl isocyanate to give the title compound (64%) as a white powder. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.90 (1H, s), 7.64 (1H, d, J = 6.6 Hz), 7.52 (1H, m), 7.34-7.20 (7H, m), 5.01 (2H, s), 3.83 (2H, t, J = 7.6 Hz), 1.56 (1H, m), 1.41 (2H, m), 0.92 (6H, d, J = 6.6 Hz).

Example 8

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-(4-methoxybenzyl)-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

Sodium hydride (0.057 g, 1.43 mmol) was added to a stirred suspension of ± ethyl 2-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-3-(3-methylbutylamino)-3-oxopropionate (0.214 g, 0.561 mmol) in tetrahydrofuran (6 mL) under argon, followed by 4-methoxybenzyl isocyanate (0.160 mL, 1.12 mmol). The mixture was heated under reflux for 3 h, then cooled. Saturated aqueous NH_4Cl (30 mL) was added and the mixture extracted with ethyl acetate. The extracts were washed (water, brine), dried ($MgSO_4$), evaporated under reduced pressure, then the residue chromatographed (silica gel, 60-80% ethyl acetate/hexanes) to give the title compound (0.270 g, 96%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 13.90 (1H, s) 7.64 (1H, dd, J = 7.7, 1.4 Hz), 7.52 (1H, m), 7.25 (4H, m), 6.86 (2H, d, J = 8.8 Hz), 4.93 (2H, s), 3.82 (2H, m), 3.72 (3H, s), 1.57 (1H, m), 1.41 (2H, m), 0.92 (6H, d, J = 6.5 Hz).

Example 9

1,3-Dibenzyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione

Sodium hydride (60% in mineral oil, 0.224 g, 5.59 mmol) was added to a stirred suspension of (1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)acetic acid, ethyl ester (0.500 g, 1.86 mmol) in tetrahydrofuran (20.0 mL) under argon. After 5 min, benzyl isocyanate (0.690 mL, 5.59 mmol) was added, and the reaction was heated under reflux for 3 h, then cooled and diluted with 1M aqueous HCl (20 mL). Tetrahydrofuran was removed under reduced pressure and the solid filtered, washed (water) and dried. The crude product was boiled in ethyl acetate and ether (1:1, 20 mL), cooled, filtered, washed with ether, and dried to leave the title compound (0.72 g, 79%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 7.73 (1H, d, J = 7.9 Hz), 7.6 (1H, m), 7.34 (2H, m), 7.29-7.21 (10H, m), 5.04 (4H, s).

Example 10

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

Water (2 mL) was added slowly to a stirred solution of 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-(4-methoxybenzyl)-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione (example 8, 0.661 g, 1.32 mmol) in H_2SO_4 (10.0 mL) cooled in a cold water bath. The mixture was stirred at room temperature for 3 h, then poured over ice. The product was extracted with ethyl acetate and the extracts were washed (brine), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (silica gel, 0-15% methanol/dichloromethane) to give a slightly impure product which was reprecipitated from hot methanol with water to give the title compound (0.225 g, 56%) as a solid. ^{1}H NMR (300MHz, d_6-DMSO) δ 7.81 (1H, d, J =7.8 Hz), 7.67 (1H, m), 7.44 (2H, m), 3.76 (2H, m), 1.58 (1H, m), 1.42 (2H, m), 0.92 (6H, d, J = 6.6 Hz).

Example 11

1-Carboxymethyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

A mixture of 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione (Example 10, 0.052 g, 0.137 mmol), ethyl bromoacetate (0.066 g, 0.395 mmol) and potassium carbonate (0.055 g, 0.398 mmol) in dimethylformamide (1.0 mL) was heated at 100°C for 18h. The reaction was then cooled, treated with 1M aqueous HCl (10 mL) and extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography (silica gel, 20-100% ethyl acetate/hexanes) gave the ethyl ester of the title compound in an impure state. 1M aqueous NaOH (1.0 mL, 1.00 mmol)) was added to a solution of the crude ester in methanol (5.0 mL) dropwise at room temperature and the mixture stirred for 18h, then acidified with 1M aqueous HCl and extracted with ethyl acetate. The extracts were washed (brine), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was reprecipitated from hot methanol with water and a small amount of aqueous HCl. The solid was filtered, washed with aqueous HCl, and dried to give the title compound (0.010 g, 15%) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 13.63 (1H, s), 7.68 (1H, d, J = 6.6 Hz), 7.57 (1H, m), 7.31 (2H, m), 4.46 (2H, s), 3.83 (2H, m), 1.58 (1H, m), 1.43 (2H, m), 0.92 (6H, d, J = 6.6 Hz).

Example 12

1-(2-Cyanobenzyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

Sodium hydride (60% in mineral oil, 0.013 g, 0.318 mmol) was added to a stirred solution of 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione (Example 10, 0.060 g, 0.159 mmol) and 2-cyanobenzylbromide (0.093 g, 0.474 mmol) in dimethylformamide (0.5 mL) and the mixture heated in a microwave synthesiser for 10 min at 100°C. The reaction was cooled and poured into 1M aqueous HCl (10 mL), then extracted with ethyl acetate. The extracts were washed (H_2O, brine), dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography (silica gel, 20-100% ethyl acetate/hexanes) gave the title compound (0.072 g, 92%) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 13.70 (1H, s), 7.82 (1H, d, J = 6.1 Hz), 7.64 (2H, m). 7.52 (1H, m), 7.44 (1H, m), 7.31-7.14 (3H, m), 5.17 (2H, s), 3.86 (2H, m), 1.58 (1H, m), 1.44 (2H, m), 0.92 (6H, d, J = 6.6 Hz).

Example 13

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2-methylpropyl)-1*H*-pyrimidine-2,4-dione

Sodium hydride (0.013 g of a 60% oil suspension, 0.325 mmol) was added to a stirred mixture of 5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione (Example 10, 0.060 g, 0.159 mmol), 2-methylpropyl bromide (0.065 g, 0.474 mmol) and potassium iodide (0.026 g, 0.158 mmol) in dimethylformamide (0.5 mL) and the mixture heated in a microwave synthesiser for 1 h at 100°C. The reaction was cooled and poured into 1M aqueous HCl (10 mL), then extracted with ethyl acetate. The extracts were washed (H_2O, brine), dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography (silica gel, 20-100% ethyl acetate/hexanes) gave a product that was triturated with ether to give the title compound (0.035 g, 51%) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 13.90 (1H, s), 7.65 (1H, m), 7.51 (2H, m), 7.28-7.23 (2H, m), 3.82 (2H, m), 3.65 (2H, d, J = 7.4 Hz), 2.05 (1H, m), 1.55 (1H, m), 1.40 (2H, m), 0.91 (6H, d, J = 6.6 Hz), 0.83 (6H, d, J = 6.8 Hz).

Example 14

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-isopropyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

Sodium hydride (0.025 g, 0.625 mmol) was added to a stirred mixture of ± ethyl 2-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-3-(3-methylbutylamino)-3-

oxopropionate (0.080 g, 0.210 mmol) and isopropyl isocyanate (0.054 g, 0.630 mmol) in tetrahydrofuran (1 mL). After the effervescence had finished, the mixture was heated in a microwave synthesiser at 80°C for 30 min, then cooled. 1M aqueous HCl (10 mL) was added and the mixture extracted with ethyl acetate. The extracts were washed (water, brine), dried ($MgSO_4$), evaporated under reduced pressure, then the residue chromatographed (silica gel, 20-100% ethyl acetate/hexanes). The partially purified material was reprecipitated from methanol with water, filtered, washed (water), and dried to leave the title compound (0.035 g, 40%) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 13.70 (1H, s), 7.82 (1H, d, J = 7.1 Hz), 7.66 (1H, m), 7.50 (1H, m), 7.42 (1H, m), 5.14 (1H, m), 3.85 (2H, m), 1.60 (1H, m), 1.45 (2H, m), 1.41 (6H, d, J = 6.9 Hz), 0.94 (6H, d, J = 6.6Hz).

Example 15

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-methyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione

The procedure of Example 14 was followed here, using methyl isocyanate in place of isopropyl isocyanate, to give the title compound (65%) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 13.70 (1H, s), 7.78 (1H, d, J = 6.8 Hz), 7.64 (1H, m), 7.44 (1H, d, J = 8.0 Hz), 7.39 (1H, m), 3.84 (2H, m), 3.20 (3H, s), 1.59 (1H, m), 1.44 (2H, m), 0.93 (6H, d, J = 6.6 Hz).

Example 16

5-(1,1-Dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrimidine-2,4-dione

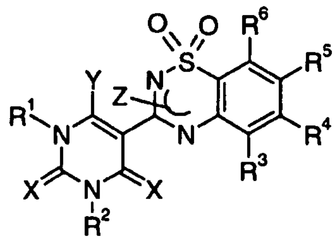
The procedure of Example 13 was followed here, using 2-bromo-1,1,1-trifluoroethane in place of 2-methylpropyl bromide, to give the title compound (28%) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 13.55 (1H, s), 7.69 (1H, m), 7.54 (1H, m), 7.32-7.29 (2H, m), 4.63 (2H, q, J = 9.2 Hz), 3.84 (2H, m), 1.58 (1H, m), 1.43 (2H, m), 0.92 (6H, d, J = 6.6 Hz).

The HCV NS5B inhibitory activity of the compounds of Formula (I) was determined using standard procedures well known to those skilled in the art and described in, for example Behrens et al., EMBO J. 15:12-22 (1996), Lohmann et al., Virology 249:108-118 (1998) and Ranjith-Kumar et al., J. Virology 75:8615-8623 (2001).

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

What is claimed is:

1. A compound according to Formula:



I

wherein:

R^1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C(O)OR^7, -C(O)R^7, and -C(O)NR^{7}R^8 , where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC$_1$-C$_4$ alkyl, -SC$_1$-C$_4$ alkyl, -NR^{8}R^9, cyano, nitro, -CO$_2$R^8, -C(O)OC$_1$-C$_4$ alkyl, -CONR^{8}R^9, -CONH$_2$, aryl, and heteroaryl, or said cycloalkyl, heterocycloalkyl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, -NH$_2$, -OC$_1$-C$_4$ alkyl, -SC$_1$-C$_4$ alkyl, -N(C$_1$-C$_4$ alkyl)(C$_1$-C$_4$ alkyl), -NH(C$_1$-C$_4$ alkyl), cyano, nitro, -CO$_2$H, -C(O)OC$_1$-C$_4$ alkyl, -CON(C$_1$-C$_4$ alkyl)(C$_1$-C$_4$ alkyl), -CONH(C$_1$-C$_4$ alkyl) and -CONH$_2$;

R^2 is hydrogen, -C(O)OR^9, C_2-C_{10} alkyl, C_2-C_{10}alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, -(C$_1$-C$_6$ alkyl)-(C$_3$-C$_6$ cycloalkyl), -(C$_2$-C$_6$ alkenyl)-(C$_3$-C$_6$ cycloalkyl), -(C$_2$-C$_6$ alkynyl)-(C$_3$-C$_6$ cycloalkyl), -(C$_1$-C$_6$ alkyl)-heterocycloalkyl, -(C$_2$-C$_6$ alkenyl)-heterocycloalkyl, -(C$_2$-C$_6$ alkynyl)-heterocycloalkyl, -(C$_1$-C$_6$ alkyl)-aryl, (C$_2$-C$_6$ alkenyl)-aryl, -(C$_2$-C$_6$ alkynyl)-aryl, -(C$_1$-C$_6$ alkyl)-heteroaryl, -(C$_2$-C$_6$ alkenyl)-heteroaryl, or -(C$_2$-C$_6$ alkynyl)-heteroaryl,

where said C_2-C_{10} alkyl, C_2-C_{10}alkenyl, C_2-C_{10} alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, -OH, -OC$_1$-C$_4$ alkyl, -SH, -SC$_1$-C$_4$ alkyl, -S(O)(C$_1$-C$_4$ alkyl), -SO$_3$H, and -S(O)$_2$(C$_1$-C$_4$ alkyl),

said C_3-C_6 cycloalkyl is unsubstituted or substituted with one or more substituents independently selected from halogen, cyano, C_1-C_4 alkyl, -OH, -OC$_1$-C$_4$ alkyl, -SH, -SC$_1$-C$_4$ alkyl, -S(O)(C$_1$-C$_4$ alkyl), -SO$_3$H, and -S(O)$_2$(C$_1$-C$_4$ alkyl),

or the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of said -(C$_1$-C$_6$ alkyl)-(C$_3$-C$_6$ cycloalkyl), -(C$_2$-C$_6$ alkenyl)-(C$_3$-C$_6$ cycloalkyl), -(C$_2$-C$_6$ alkynyl)-(C$_3$-C$_6$ cycloalkyl), -(C$_1$-C$_6$ alkyl)-heterocycloalkyl,

-(C_2-C_6 alkenyl)-heterocycloalkyl, -(C_2-C_6 alkynyl)-heterocycloalkyl, -(C_1-C_6 alkyl)-aryl, (C_2-C_6 alkenyl)-aryl, -(C_2-C_6 alkynyl)-aryl, -(C_1-C_6 alkyl)-heteroaryl, -(C_2-C_6 alkenyl)-heteroaryl, or -(C_2-C_6 alkynyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, cyano, nitro, -OH, -NH_2, -OC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -NH(C_1-C_4 alkyl);

R^3 and R^4 are each independently selected from the group consisting of hydrogen, halogen, cyano, C_1-C_6 alkyl, -OH, and -OC_1-C_4 alkyl;

R^5 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, nitro, cyano, halogen, -C(O)OR^7, -C(O)R^7, -C(O)NR^7R^8, -OR^7, -SR^7, -S(O)R^{10}, -S(O)$_2R^{10}$, -NR^7R^8, protected -OH, -N(R^8)C(O)R^7, -OC(O)NR^7R^8, -N(R^8)C(O)NR^7R^8, -P(O)(OR^7)$_2$, -$SO_2NR^7R^8$, -SO_3H, or -N(R^8)SO_2R^{10},

where said C_1-C_8 alkyl, C_2-C_8 alkenyl or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -SH, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -NR^8R^9, cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -$CONR^8R^9$, -$CONH_2$, aryl, heteroaryl, heterocycloalkyl, -C(O)aryl, -C(O)heterocycloalkyl, and -C(O)heteroaryl, where said aryl, heteroaryl, heterocycloalkyl, aryl, -C(O)aryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano and nitro,

or said cycloalkyl, heterocycloalkyl, aryl or heteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen, -OH, -SH, -NH_2, -OC_1-C_4 alkyl, -SC_1-C_4 alkyl, -N(C_1-C_4 alkyl)(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), cyano, nitro, -CO_2H, -C(O)OC_1-C_4 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl) and -$CONH_2$;

R^6 is hydrogen, halogen, C_1-C_4 alkyl, or -OR^7;

or R^3 and R^4 or R^4 and R^5 or R^5 and R^6 taken together are alkylenedioxy;

X is O or S;

Y is -OH or -SH;

Z is hydrogen or C_1-C_4 alkyl;

wherein each R^7 is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, and -C_1-C_6 alkyl-heteroaryl, -C_2-C_6 alkenyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkenyl-heterocycloalkyl, -C_2-C_6 alkenyl-aryl, -C_2-C_6 alkenyl-heteroaryl, -C_2-C_6 alkynyl-C_3-C_8 cycloalkyl, -C_2-C_6 alkynyl-heterocycloalkyl, -C_2-C_6 alkynyl-aryl, and -C_2-C_6 alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OR^9, -NR^8R^9, cyano, nitro, -CO_2R^9, -$CONR^8R^9$, -$NR^8CONR^8R^9$, -$OCONR^8R^9$, -$SO_2NR^8R^9$, and -COR^9,

or any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said -C_1-C_6 alkyl-C_3-C_8 cycloalkyl, -C_1-C_6 alkyl-heterocycloalkyl, -C_1-C_6 alkyl-aryl, or -C_1-C_6 alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, -OR^9, -NR^8R^9, cyano, nitro, -CO_2R^9, -$CONR^8R^9$, -$NR^8CONR^8R^9$, -$OCONR^8R^9$, -$SO_2NR^8R^9$, and -COR^9;

each R^8 is independently selected from hydrogen and C_1-C_6 alkyl;

each R^9 is independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -C_1-C_4 alkyl-C_3-C_8 cycloalkyl, -C_1-C_4 alkyl-heterocycloalkyl, -C_1-C_4 alkyl-aryl, or -C_1-C_4 alkyl-heteroaryl

where said cycloalkyl, heterocycloalkyl, aryl , heteroaryl, -alkylcycloalkyl, -alkylheterocycloalkyl, -alkylaryl or -alkylheteroaryl is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, cyano, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2C_1-C_6 alkyl, -CO_2H, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), and -$CONH_2$;

or, when present in any NR^7R^8 or NR^8R^9, each R^7 and R^8 or each R^8 and R^9, independently, taken together with the nitrogen to which they are attached represent a 3-6-membered saturated ring optionally containing one other heteroatom selected from oxygen and nitrogen, where said 3-6-membered ring is unsubstituted or substituted with one or more substituents independently selected from hydrogen, C_1-C_6 alkyl, halogen, cyano, -OC_1-C_6 alkyl, -OH, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2H, -C(O)OC_1-C_6 alkyl, -C(O)C_1-C_6 alkyl, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), -$CONH_2$, C_3-C_6 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_3-C_6 cycloalkyl-C_1-C_6 alkyl-, heterocycloalkyl-C_1-C_6 alkyl-, aryl-C_1-C_6 alkyl- and heteroaryl-C_1-C_6 alkyl-, and where said cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl-, heterocycloalkylalkyl-, arylalkyl- or heteroarylalkyl- is unsubstituted or substituted with one or more substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, halogen -OC_1-C_6 alkyl, -OC_1-C_6 haloalkyl, cyano, -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -NH_2, -CO_2C_1-C_6 alkyl, -CO_2H, -CON(C_1-C_6 alkyl)(C_1-C_6 alkyl), -CONH(C_1-C_6 alkyl), and -$CONH_2$;

each R^{10} is independently selected from the group consisting of C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

$-C_1-C_6$ alkyl-C_3-C_8 cycloalkyl, $-C_1-C_6$ alkyl-heterocycloalkyl, $-C_1-C_6$ alkyl-aryl, and $-C_1-C_6$ alkyl-heteroaryl, $-C_2-C_6$ alkenyl-C_3-C_8 cycloalkyl, $-C_2-C_6$ alkenyl-heterocycloalkyl, $-C_2-C_6$ alkenyl-aryl, $-C_2-C_6$ alkenyl-heteroaryl, $-C_2-C_6$ alkynyl-C_3-C_8 cycloalkyl, $-C_2-C_6$ alkynyl-heterocycloalkyl, $-C_2-C_6$ alkynyl-aryl, and $-C_2-C_6$ alkynyl-heteroaryl,

where said C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, $-OR^{11}$, $-NR^8R^{11}$, cyano, nitro, $-CO_2R^{11}$, $-CONR^8R^{11}$, $-NR^8CONR^8R^{11}$, $-OCONR^8R^{11}$, $-SO_2NR^8R^{11}$, and $-COR^{11}$,

and where any of said cycloalkyl, heterocycloalkyl, aryl or heteroaryl (including the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moieties of said $-C_1-C_6$ alkyl-C_3-C_8 cycloalkyl, $-C_1-C_6$ alkyl-heterocycloalkyl, $-C_1-C_6$ alkyl-aryl, or $-C_1-C_6$ alkyl-heteroaryl) is unsubstituted or substituted with one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, $-OR^{11}$, $-NR^8R^{11}$, cyano, nitro, $-CO_2R^{11}$, $-CONR^8R^{11}$, $-NR^8CONR^8R^{11}$, $-OCONR^8R^{11}$, $-SO_2NR^8R^{11}$, and $-COR^{11}$;

each R^{11} is independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, heterocycloalkyl, aryl, heteroaryl, $-C_1-C_6$ alkyl-C_3-C_8 cycloalkyl, $-C_1-C_6$ alkyl-heterocycloalkyl, $-C_1-C_6$ alkyl-aryl, and $-C_1-C_6$ alkyl-heteroaryl;

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

2. The compound according to claim 1, wherein R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, carboxy-C_1-C_4 alkyl, unsubstituted aryl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and cyano.

3. The compound according to claim 1, wherein R^1 is H, $-CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, $-(CH_2)_2CH(CH_3)_2$, $-CH_2CO_2H$, $-(CH_2)_3CO_2H$, $-CH_2CH(CH_3)_2$, -phenyl, $-CH_2$(phenyl), (4-OCH_3-phenyl)CH_2-, and (2-CN-phenyl)CH_2-.

4. The compound according to claim 1, wherein R^2 is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, $-(C_1-C_2$ alkyl)-$(C_3-C_6$ cycloalkyl), $-(C_1$ alkyl)-heterocycloalkyl, $-(C_1$ alkyl)-aryl, or $-(C_1$ alkyl)-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, $-OCH_3$, $-SCH_3$, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the $-(C_1-C_4$ alkyl)-$(C_3-C_6$ cycloalkyl), $-(C_1-C_4$ alkyl)-heterocycloalkyl, $-(C_1-C_4$ alkyl)-aryl, or $-(C_1-C_4$ alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents

independently selected from $-CH_3$, halogen, nitro, cyano, -OH, $-O(C_1-C_4$ alkyl), $-NH_2$, $-NH(C_1-C_4$ alkyl) and $-N(C_1-C_4$ alkyl)(C_1-C_4 alkyl).

5. The compound according to claim 1, wherein R^2 is C_2-C_6 alkyl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, and cyano.

6. The compound according to claim 1, wherein R^2 is $-(CH_2)_2CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-CH_2$(phenyl).

7. The compound according to claim 1, wherein R^3 is H, halogen, C_1-C_4 alkyl, $-OCH_3$ or -OH.

8. The compound according to claim 1, wherein R^4 is H, halogen, $-OCH_3$ or -OH.

9. The compound according to claim 1, wherein R^5 is hydrogen, halogen, C_1-C_2 alkyl, C_2 alkenyl, $-C(O)OR^a$, $-C(O)R^a$, $-OR^b$, $-NR^aR^d$, $-C(O)NR^aR^d$, where said alkyl or alkenyl is unsubstituted or substituted with a substituent selected from $-NH_2$, $-CONH_2$ and 5-6 membered heterocycloalkyl or heteroaryl, R^a is H or methyl, R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1-C_2$ alkyl, $-CON(C_1-C_4$ alkyl)(C_1-C_4 alkyl), $-CONH(C_1-C_4$ alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, $-NH_2$, and $-CONH_2$, R^d is H or C_1-C_2 alkyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl, or R^a and R^d taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycloalkyl ring, which optionally contains an additional nitrogen heteroatom and which is unsubstituted or substituted with $-C(O)C_1-C_2$ alkyl.

10. The compound according to claim 1, wherein R^6 is hydrogen, halogen, C_1-C_4 alkyl or $-OR^{b'}$, where $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, $-NH_2$, $-CO_2H$, $-CONH_2$, $-C(O)OC_1-C_2$ alkyl, $-CON(C_1-C_4$ alkyl)(C_1-C_4 alkyl), and $-CONH(C_1-C_4$ alkyl).

11. The compound according to claim 1, wherein R^3, R^4, R^5, and R^6 are each H.

12. The compound according to claim 1, wherein X is O, Y is OH.

13. The compound according to claim 1, wherein Z is H.

14. The compound according to claim 1, wherein R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, carboxy-C_1-C_4 alkyl, unsubstituted aryl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and cyano; R^2 is C_4-C_6 alkyl, C_4 alkenyl, C_4 alkynyl, -(C_1-C_2 alkyl)-(C_3-C_6 cycloalkyl), -(C_1 alkyl)-heterocycloalkyl, -(C_1 alkyl)-aryl, or -(C_1 alkyl)-heteroaryl, where the C_4-C_6 alkyl, C_4 alkenyl or C_4 alkynyl is unsubstituted or substituted with one or more substituents independently selected from halogen, -OH, -OCH_3, -SCH_3, and where the cycloalkyl, heterocycloalkyl, aryl or heteroaryl moiety of the -(C_1-C_4 alkyl)-(C_3-C_6 cycloalkyl), -(C_1-C_4 alkyl)-heterocycloalkyl, -(C_1-C_4 alkyl)-aryl, or -(C_1-C_4 alkyl)-heteroaryl is unsubstituted or substituted with one or more substituents independently selected from -CH_3, halogen, nitro, cyano, -OH, -O(C_1-C_4 alkyl), -NH_2, -NH(C_1-C_4 alkyl) and -N(C_1-C_4 alkyl)(C_1-C_4 alkyl); R^3 is H, halogen, C_1-C_4 alkyl, -OCH_3 or -OH; R^4 is H, halogen, -OCH_3 or -OH; R^5 is hydrogen, halogen, C_1-C_2 alkyl, C_2 alkenyl, -C(O)OR^a, -C(O)R^a, -OR^b, -NR^aR^d, -C(O)NR^aR^d, where said alkyl or alkenyl is unsubstituted or substituted with a substituent selected from -NH_2, -$CONH_2$ and 5-6 membered heterocycloalkyl or heteroaryl, R^a is H or methyl, R^b is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -NH_2, -CO_2H, -$CONH_2$, -C(O)OC_1-C_2 alkyl, -CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), monocyclic heteroaryl, -C(O)monocyclic heterocycloalkyl, and -C(O)monocyclic heteroaryl, where said heteroaryl, -C(O)heterocycloalkyl, or -C(O)heteroaryl are unsubstituted or substituted one or more of C_1-C_4 alkyl, halogen, cyano, -OH, -NH_2, and -$CONH_2$, R^d is H or C_1-C_2 alkyl, where the C_1-C_2 alkyl is unsubstituted or substituted by a substituent selected from the group consisting of cyano and unsubstituted aryl, or R^a and R^d taken together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycloalkyl ring, which optionally contains an additional nitrogen heteroatom and which is unsubstituted or substituted with -C(O)C_1-C_2 alkyl; R^6 is hydrogen, halogen, C_1-C_4 alkyl or -$OR^{b'}$, where $R^{b'}$ is H or C_1-C_4 alkyl, where the C_1-C_4 alkyl is optionally unsubstituted or substituted by a substituent selected from the group consisting of cyano, -NH_2, -CO_2H, -$CONH_2$, -C(O)OC_1-C_2 alkyl,

-CON(C_1-C_4 alkyl)(C_1-C_4 alkyl), and -CONH(C_1-C_4 alkyl); X is O; Y is OH; and Z is H or methyl.

15. The compound according to claim 1, wherein R^1 is hydrogen, C_1-C_6 alkyl, C_1-C_4 haloalkyl, carboxy-C_1-C_4 alkyl, unsubstituted aryl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen and cyano; R^2 is C_2-C_6 alkyl or arylC_1-C_2 alkyl-, where the aryl of said arylalkyl is unsubstituted or substituted by one or more substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, and cyano; R^3, R^4, R^5, and R^6 are each H; X is O; Y is OH and Z is H.

16. The compound according to claim 1, wherein R^1 is H, $-CH_3$, $-CH_2CF_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, $-(CH_2)_2CH(CH_3)_2$, $-CH_2CO_2H$, $-(CH_2)_3CO_2H$, $-CH_2CH(CH_3)_2$, -phenyl, $-CH_2$(phenyl), (4-OCH_3-phenyl)CH_2-, and (2-CN-phenyl)CH_2-; R^2 is $-(CH_2)_2CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-CH_2$(phenyl); R^3, R^4, R^5, and R^6 are each H; X is O; Y is OH; and Z is H.

17. A compound

3-butyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione,

1,3-dibutyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-propyl-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1,3-bis-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1-(3-carboxypropyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-phenyl-1*H*-pyrimidine-2,4-dione,

1-benzyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H* –pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-(4-methoxybenzyl)-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1,3-dibenzyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1-carboxymethyl-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

1-(2-cyanobenzyl)-5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2-methylpropyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-isopropyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-methyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, or

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrimidine-2,4-dione,

or a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof.

18. A compound according to claim 17,

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1,3-bis-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione;

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-(4-methoxybenzyl)-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione;

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-3-(3-methylbutyl)-1-(2-methylpropyl)-1*H*-pyrimidine-2,4-dione, or

5-(1,1-dioxo-1,4-dihydrobenzo[1,2,4]thiadiazin-3-yl)-6-hydroxy-1-isopropyl-3-(3-methylbutyl)-1*H*-pyrimidine-2,4-dione, or a salt or solvate thereof.

19. A pharmaceutically acceptable salt of the compound according to claim 17 or 18, or tautomer thereof, wherein said pharmaceutically acceptable salt is a sodium salt or a potassium salt.

20. A method of inhibiting an RNA-containing virus which comprises contacting said virus with an effective amount of the compound according to any one of claims 1 to 19.

21. A method of treating infection caused by an RNA-containing virus which comprises administering to a subject in need thereof an effective amount of the compound according to any one of claims 1 to 19.

22. A method according to claim 21 comprising treating an HCV infection.

23. A method according to claim 20 or claim 21 comprising inhibiting hepatitis C virus.

24. A method according to claim 21, wherein said HCV infection is acute hepatitis infection, chronic hepatitis infection, hepatocellular carcinoma or liver fibrosis.

25. A method according to claim 21 comprising treating an infection caused by Dengue, HIV or a picornavirus.

26. A method according to claim 21 comprising administering said compound in combination with one or more agents selected from the group consisting of an immunomodulatory agent and an antiviral agent.

27. A method according to claim 26 wherein the immunomodulatory agent is selected from the group consisting of alpha interferon, beta interferon, gamma interferon, a cytokine, a vitamin, a nutritional supplement, an antioxidant compound, a vaccine and a vaccine comprising an antigen and an adjuvant.

28. A method according to claim 21 comprising administering said compound in combination with an interferon.

29. A method according to claim 21 comprising administering said compound in combination with an interferon and ribavirin.

30. A method according to claim 21 comprising administering said compound in combination with an interferon and levovirin.

31. A method according to claim 21 comprising administering said compound in combination with an HCV antisense agent.

32. A method according to claim 21 comprising administering said compound in combination with an immunoglobulin, a peptide-nucleic acid conjugate, an oligonucleotide, a ribozyme, a polynucleotide, an anti-inflammatory agent, a pro-inflammatory agent, an antibiotic or a hepatoprotectant.

33. A method for inhibiting replication of hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, said method comprising contacting a cell infected with said virus with an effective amount of the compound according to any one of claims 1 to 19.

34. A method of treating infection caused by hepatitis C virus comprising inhibiting replication of both positive and negative strand HCV-RNA, said method comprising administering to a subject in need thereof an effective amount of the compound according to any one of claims 1 to 19.

35. The method according to claim 33, wherein said compound substantially equally inhibits positive strand HCV-RNA replication and negative strand HCV-RNA replication.

36. The method according to claim 34, wherein said compound substantially equally inhibits positive strand HCV-RNA replication and negative strand HCV-RNA replication.

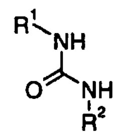
37. Use of the compound according to claim 1, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament for the treatment of an RNA-containing virus.

38. Use of the compound according to claim 1, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits hepatitis C virus.

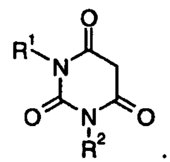
39. Use of the compound according to claim 1, a tautomer thereof, or a pharmaceutically acceptable salt or solvate thereof, in the preparation of a medicament that inhibits replication of both positive and negative strand HCV-RNA.

40. A process for the preparation of the compound according to claim 1 comprising.

a) treating a urea having the formula:

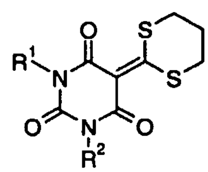


with a malonic acid di-ester to form a compound having the formula:



;

b) converting the compound formed in step a) into a compound having the formula:

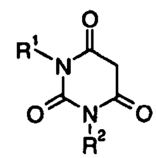


;

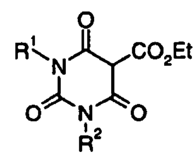
c) converting the compound formed in step b) into said compound.

41. A process for the preparation of the compound according to claim 1 comprising.

a) converting a compound having the formula



into a compound having the formula:

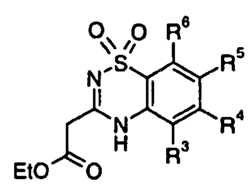


;and

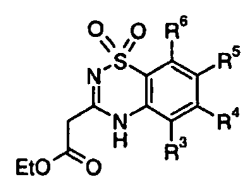
b) converting the compound formed in step a) into the compound of Formula I.

42. A process for the preparation of the compound according to claim 1 comprising.

a) converting a compound having the formula



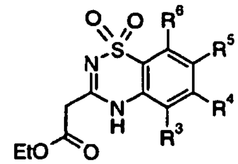
into a compound having the formula:



;and

b) converting the compound formed in step a) into the compound of Formula I.

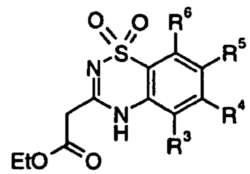
43. A process for the preparation of the compound according to claim 1 comprising converting a compound having the formula.



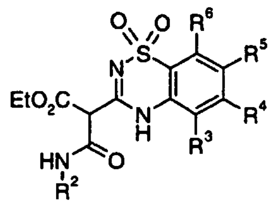
into the compound of Formula I.

44. A process for the preparation of the compound according to claim 1 comprising.

a) converting a compound having the formula



into a compound having the formula:

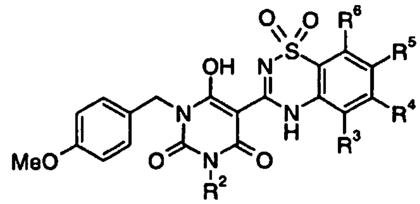


;and

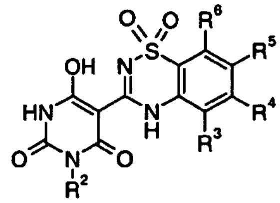
b) converting the compound formed in step a) into the compound of Formula I.

45. A process for the preparation of the compound according to claim 1 comprising.

a) converting a compound having the formula



into a compound having the formula:



;and

b) converting the compound formed in step a) into the compound of Formula I.

SEQUENCE LISTING

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<120> NOVEL ANTI-INFECTIVES

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<151> 2001-10-29

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: NOVEL ANIT-INFECTIVES

(57) Abstract: Disclosed are compounds useful as HCV anti-infectives and methods of making and using the same.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/34655

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 285/24; A61K 31/549; A61P 31/12
US CL : 544/12; 514/223.2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/12; 514/223.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,029,780 A (NISHIMURA et al) 14 June 1977 (14.06.1977). See entire document.	
A	US 4,025,508 A (PERRAULT) 24 May 1977 (24.05.1977) see entire document.	1-19 and 37-45

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 31 March 2003 (31.03.2003)	Date of mailing of the international search report 15 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Della Collins for Venkataraman Balasubramanian Telephone No. (703)308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/34655

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claim Nos.: 20-36
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.